IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

April 19, 2004

In re Application of:	Santos *et al.*
Serial No.	10/017,697
Filed:	July 20, 2001
For:	**TASTE MASKED AQUEOUS LIQUID PHARMACEUTICAL COMPOSITION**
Examiner:	Fubara, Blessing M.
Art Unit:	1615
Attorney Docket No.:	DIZ-1
Confirmation No.:	5711

DECLARATION UNDER 37 CFR § 1.132

HONORABLE COMMISSIONER OF
PATENTS AND TRADEMARKS
Washington, D.C. 20231

In response to the Office Action dated December 30, 2003, I, Kennie U. Dee, Ph.D., hereby declare and say as follows:

BACKGROUND INFORMATION

1. I am employed at United Laboratories, Inc. My *curriculum vitae*, which describes my education, employment, research publications and other expert qualifications, is attached hereto as Exhibit 1.

2. I have extensive experience in the fields of food and pharmaceutical science. I have worked in the field of pharmaceutical science since 1998. Through my years of research and professional activities in the fields of food and pharmaceutical dosage form development, I am familiar with the skills of those working in the field from 1998 to the present. In carrying out my current professional activities, I keep up to date on the technical literature and maintain contact with other experts in the field.

3. I am a co-inventor of the invention of claims 1-46 in the present patent application, Ser. No. 10/017,697.

4. I have read and understood the above referenced patent application, including the specification, claims and the relevant prior art, as well as U.S. Patent No. 5,431,916 to White, cited by the Examiner in this case in support of the anticipation and obviousness rejections of the claims. Based on my analysis of the contents of the aforementioned documents, I have formulated certain opinions regarding the alleged anticipation and obviousness of the claims.

5. The standard I used for anticipation was whether a single prior art reference discloses each and every element or limitation of the claim.

6. The standard I used for obviousness was whether the differences between the subject matter sought to be patented and the prior art are such that the claimed subject matter as a whole would have been obvious, at the time the invention was made, to a person having ordinary skill in the art of pharmaceutical dosage form development, and whether the teaching or suggestion is accompanied by an expectation of successfully making the claimed subject matter.

7. A person of ordinary skill in the art would have a Ph.D. in pharmacy, pharmacology or medicinal chemistry, or an equivalent degree and at least two years of laboratory research experience in pharmacology, medicinal chemistry or pharmaceutical dosage form development, or at least a B.S. degree and a minimum of four years of laboratory research experience in pharmacology, medicinal chemistry or pharmaceutical dosage form development.

NOVELTY OF CLAIMS 1-4, 7-8, 10-11, 13, 15-19, 22-24, 28-33 and 43-46

8. The Examiner maintains that U.S. Patent No. 5,431,916 to White anticipates claims 1-4, 7-8, 10-11, 13, 15-19, 2-24, 28-33 and 43-46. I strongly disagree with the Examiner's conclusion, as explained in further detail below.

9. Amended claims 1 and 43 in application Ser. No. 10/017,697 recite a taste-masked liquid pharmaceutical composition, and a method for preparing a taste-masked liquid pharmaceutical composition. Both claims 1 and 43, as amended, expressly recite that the pharmaceutical composition in its final form is a liquid, which is administered to the patient.

10. The taste-masked liquid pharmaceutical composition described in application Ser. No. 10/017,697 successfully masks both the initial bitterness perception as well as the unpleasant lingering bitter aftertaste generally perceived in oral liquid pharmaceutical compositions containing bitter drugs. Most taste masking techniques in the prior art are only able to mask the initial bitterness perception and fail to reduce or eliminate the bitter aftertaste.

11. White (U.S. 5,431,916) does not disclose a taste-masked liquid pharmaceutical composition. Rather, the pharmaceutical compositions disclosed by White are encapsulated and thus are not administered in liquid form.

12. Soft gelatin capsules are one-piece soft gelatin shells hermetically sealed to enclose a liquid or a semi-liquid fill. The liquid or semi-liquid composition is filled and sealed into the soft

gelatin capsules while hot. The soft gelatin shell protects and prevents the tongue's taste buds from perceiving the taste of the liquid or semi-liquid fill. This objective is similarly achieved with hard gelatin capsules and coated tablets. Indeed, most of the examples disclosed by White are compositions and methods for manufacture of pharmaceuticals that are encapsulated within soft gelatin capsules.

13. Upon testing in the laboratory, White's composition was noted to be in liquid form only at temperatures above about 50°C. Below this temperature, White's composition solidifies into a hard mass. At room temperature, a condition at which oral liquid pharmaceutical compositions are generally administered, White's composition is not a liquid pharmaceutical composition.

14. Furthermore, the pharmaceutical compositions disclosed by White are not taste-masked liquids. Indeed, upon testing, our laboratory determined that the compositions of White are unacceptably bitter. Results of the laboratory trials are attached hereto as Exhibit 2.

15. While White specifies that tri-esters are an essential component of his composition and while the comprising language of the instant claims does not exclude the tri-ester of White from the instant claimed invention, it would be obvious to a person having ordinary skill in the art that the tri-ester is not an essential component of the instant invention, nor is it a component that is of functional use in oral liquid pharmaceutical compositions. Tri-esters are generally used as plasticizers for polymers in pharmaceutical coatings. The tri-esters are viscous liquids with a bitter taste.

16. Therefore, White (U.S. 5,431,916) does not disclose each and every element of claims 1 and 43 and their dependent claims.

NON-OBVIOUSNESS OF CLAIMS 5-6, 9, 12, 14 and 20

17. The Examiner maintains that claims 5-6, 9, 12, 14 and 20 are obvious over U.S. Patent No. 5,431,916 to White. I strongly disagree with the Examiner's conclusion of obviousness, and particularly disagree with the Examiner's assertion that one of ordinary skill in the art would have a reasonable expectation of success in making the claimed invention, as the Examiner's conclusion is not supported by any evidence and, in fact, it is incorrect, as explained in further detail below.

18. White does not provide any teaching in regard to compositions or methods for making taste-masked liquid pharmaceutical compositions whatsoever, and thus provides absolutely no teaching pertaining to taste masking or improving the taste of unpleasant tasting liquid drugs. In fact, the disclosure and claims of White are strictly limited to solvent systems

with significant solvating properties able to dissolve relatively large quantities of pharmaceutical actives at high temperature.

19. White's composition also requires the inclusion of a tri-ester, which is a clear viscous liquid with a bitter taste. Those with ordinary skill in the art would know that increasing the amount of dissolved bitter-tasting drug in a pharmaceutical composition, as presented in White's teachings, only increases the amount of bitter-tasting drug that can be detected by the human tongue's taste buds.

20. Furthermore, the use of functional ingredients with bitter taste, such as the tri-esters, is responsible for increasing the bitter taste of the pharmaceutical composition. These are contrary to the objective of taste masking.

21. The disclosure (and claims) of White are strictly limited to compositions and methods for manufacture of pharmaceuticals that are encapsulated within soft gelatin capsules. Thus, White's disclosure clearly is not sufficient to teach Applicant's claimed taste-masked liquid pharmaceutical compositions and methods for making the same.

CONCLUSION

22. Based on the above analysis, I conclude that the claims in the present patent application are both novel and non-obvious over the prior art.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Dated: APRIL 19, 2004 By: Jennie Lee

Exhibit 2

White's teachings as presented in US 5,431,916 were duplicated in the laboratory. The taste of the pharmaceutical compositions were evaluated and compared to the applicant's taste-masked aqueous liquid pharmaceutical composition.

Experiment 1

A pharmaceutical composition containing acetaminophen was prepared according to the composition and process described in White's Example VIII (US 5,431,916 column 12).

Table 1

	% w/w
Triethyl Citrate	22.86
Polyvinylpyrrolidone 17	17.14
Acetaminophen	57.14
Polyethylene Glycol 3350	2.86

Polyvinylpyrrolidone and triethyl citrate were heated with mixing at approximately 65°C. Polyethylene glycol 3350 was added and melted into solution. Acetaminophen was screened through 80 mesh and then added to the solvent blend and heated to 125°C. The resulting product was a supersaturated solution of acetaminophen . On cooling, portion of the acetaminophen comes out of solution and remains suspended. With further cooling to about 60°C, the liquid preparation solidifies into a hard mass. At room temperature, the pharmaceutical composition is not in liquid form. The taste of the warm liquid as well as the cooled solid mass were both unacceptably bitter.

The pharmaceutical composition of White's Example VIII (US 5,431,916) is intended for filling into soft gelatin capsules while hot. The final product is not a liquid at room temperature nor is it taste-masked.

Experiment 2

The effect of White's invention on the taste of a liquid suspension containing acetaminophen was determined by evaluating a composition containing triethyl citrate, polyvinylpyrrolidone and polyethylene glycol present at the same ratios used in White's example VIII.

Table 2

	Grams per 100 mL
Triethyl Citrate	2
Polyvinylpyrrolidone 17	1.5
Acetaminophen	5
Polyethylene Glycol 3350	0.25
Sucrose	85
Citric Acid-Sodium Citrate buffer	q.s. to pH 5-6
Purified Water	q.s. to 100 mL
pH	5 -- 6

Polyvinylpyrrolidone and triethyl citrate were heated with mixing at approximately 65°C. Polyethylene glycol 3350 was added and melted into solution. Acetaminophen was screened through 80 mesh and then added to the solvent blend and heated to 125°C. The warm liquid was added to sucrose syrup. The pH of the composition was adjusted to 5 to 6 with citric acid-sodium citrate buffer. Purified water was added to bring the total volume to 100 mL.

The initial taste and aftertaste of the pharmaceutical composition was unacceptably bitter. White's composition is not a taste-masked liquid pharmaceutical composition.

Experiment 3

The tri-ester is an essential component of White's invention. The effect of adding a tri-ester on the taste of a liquid suspension containing acetaminophen was determined by evaluating compositions containing 0%, 1%,, 2.5% and 10% of the tri-ester (in this case, triethyl citrate). The composition contains the tri-ester at the preferred use limits and ratio to polyvinylpyrrolidone taught in White (US 5,431,916).

Table 3

Ingredient	Example 3-A (g/100 ml)	Example 3-B (g/100 ml)	Example 3-C (g/100 ml)	Example 3-D (g/100 ml)
Acetaminophen	5	5	5	5
Triethyl citrate	-	1	2.5	10
Xanthan gum	0.3	0.3	0.3	0.3
Sucrose	55	55	55	55
70% Sorbitol Solution	10	10	10	10
Invert Sugar	20	20	20	20
Glycerin	5	5	5	5
Crospovidone (Kollidon CL-M)	2.5	2.5	2.5	2.5
Sodium Benzoate	0.2	0.2	0.2	0.2
Sorbitan Monolaurate	0.05	0.05	0.05	0.05
Disodium Edetate	0.2	0.2	0.2	0.2
Sucralose	0.2	0.2	0.2	0.2
Saccharin sodium	0.13	0.13	0.13	0.13
Coloring	0.006	0.006	0.006	0.006
Flavoring	0.3	0.3	0.3	0.3
Citric Acid	0.1	0.1	0.1	0.1
Sodium Citrate Dihydrate	0.295	0.295	0.295	0.295
Purified Water	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL	q.s. to 100 mL
pH	5 - 6	5 - 6	5 - 6	5 - 6

The acetaminophen suspensions were prepared in the following manner:

Sucrose syrup containing sodium benzoate was prepared. The hot syrup was cooled down to 30°C. The sucrose syrup, sorbitol and invert sugar were blended together to form Phase A. Sorbitan monolaurate and triethyl citrate was added to the mixture to form Phase B. Phase B was stirred for 15 minutes.

Crospovidone was dispersed into Phase B. The admixture was stirred for 30 minutes after which acetaminophen was added. The resulting admixture was stirred for one hour to form Phase C. Xanthan gum was dispersed in glycerin. The resulting dispersion was added to Phase C. The admixture was stirred for 15 minutes to form Phase D.

An aqueous solution of citric acid and sodium citrate dihydrate was prepared to form Phase E. An aqueous solution of disodium edetate, saccharin sodium and sucralose was prepared to form Phase F.

Phases E and F were added to Phase D. The admixture was stirred for one hour and then homogenized in a colloid mill. Color and flavor were added to the homogenized bulk, which was stirred for two more hours before adjusting to the desired volume with purified water. The suspensions were allowed to stand for 24 hours before tasting.

Three rounds of taste tests were done. Example 3-A was compared to Example 3-B in the first round. Example 3-B was compared to Example 3-C in round 2. Example 3-C was compared to Example 3-D in round 3. Ten respondents were asked to taste 2.5 ml of each sample in random order. The respondents were asked to drink water and take unsalted crackers between samples to remove traces of the first sample tasted. Each respondent was asked to pick a preference based on reduced bitterness. The results are presented in Tables 4, 5 and 6.

Table 4: Taste Comparison: Example 3-A vs 3-B

Example	Triethyl Citrate (% w/v)	No. of Respondents who prefer sample
3-A	0	10 out of 10
3-B	1	None

Table 5: Taste Comparison: Example 3-B vs 3-C

Example	Triethyl Citrate (% w/v)	No. of Respondents who prefer sample
3-B	1	10 out of 10
3-C	2.5	None

Table 6: Taste Comparison: Example 3-C vs 3-D

Example	Triethyl Citrate (% w/v)	No. of Respondents who prefer sample
3-C	2.5	10 out of 10
3-D	10	None

The same respondents were requested to rate the degree of bitterness of the pure tri-ester, triethyl citrate, on a scale of 1 to 5 where a rating of 1 means not bitter and rating of 5 means extremely bitter. The results are presented in Table 7.

Table 7: Respondent's perception of the degree of bitterness of Triethyl Citrate

Degree of Bitterness		No. of Respondents who rated sample
4	Extremely bitter	8 out of 10
3	Moderately bitter	2 out of 10
2	Slightly bitter	None
1	Not bitter	None

The results show that the tri-ester, triethyl citrate, does not reduce bitterness. In fact, triethyl citrate by itself is bitter and the bitter taste in these compositions is due primarily to the addition of triethyl citrate thus the increasing bitterness with higher levels of triethyl citrate.

Dr. Kennie U. Dee
Vice President - Research & Development
United Laboratories, Inc.

Education:

1992-1996: Ph.D. Chemical Engineering, Cornell University
Major Field: Biochemical Engineering; Minor: Biochemistry

Work Experience:

1990-1992: Scientist, Winton Hill Technical Center, Procter & Gamble, Cincinnati, US

1996-1997: Senior Scientist, Japanese Technical Center, Procter & Gamble, Kobe, Japan

1997-1998: Principal Scientist, Johnson & Johnson Asia-Pacific

1998-present: VP, Research & Development, United Laboratories, Inc.

Others:

Member of American Mensa

Member of American Institute of Chemical Engineers (AICHE)

Listed in "Who's Who in Science and Engineering", 6th edition

Journals:

Dee, K.U. and M.L. Shuler, *"Optimization of an Assay for Baculovirus Titer and Design of Regimens for the Synchronous Infection of Insect Cells"*, Biotechnology Progress, **13**:14-24 (1997).

Dee, K.U. and M.L. Shuler, *"A mathematical model of the trafficking of acid-dependent enveloped viruses: application to the binding, uptake, and nuclear accumulation of baculovirus"*, Biotechnology and Bioengineering, **54**(5): 468-490 (1997).

Dee, K.U., Shuler, M.L. and Wood, H.A., *"Inducing single-cell suspension of BTI-TN5B1-4 insect cells: I. The use of sulfated polyanions to prevent cell aggregation and enhance recombinant protein production"*, Biotechnology and Bioengineering, **54**(3): 191-205 (1997).

Dee, K.U., Wood, H.A. and Shuler, M.L., *"Inducing single-cell suspension of BTI-TN5B1-4 insect cells: II. The effect of sulfated polyanions on baculovirus infection"*, Biotechnology and Bioengineering, 54(3): 206-220 (1997).

Dee, Kennie U., D.A. Hammer, and M.L. Shuler, *"A model of the binding entry, uncoating, and RNA synthesis of Semliki Forest virus in Baby Hamster Kidney (BHK-21) cells"*, Biotechnology and Bioengineering, 46:485-496 (1995).

Approved Patents:

US 5728580: Method and culture media for inducing single cell suspension in insect cell lines.

US 6329330/EP 0964055: Photostable compositions.

US 6646011/EP 0962135: Insect repellant compositions.

EP 0964047: Anti-oxidant system.

Applied Patents:

US 20030118654A1: Taste masked aqueous liquid pharmaceutical composition.

US 20030191192A1: Oral suspension formulation.

US 20040009280A1: Powdered beverage mix with rapidly dissolving calcium.